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(54) Title: NOVEL METHOD AND USE

(57) Abstract: The invention relates to a method of antagonizing GLP-1 activity in a mammalian patient, comprising administering to said patient an effective amount of a compound of general formula (I): wherein R₁ and R₂ independently of each other are C₁₋₄alkyl, R₃ is halogen, hydroxy, C₁₋₄-alkoxy or trifluoromethoxy, R₄ is hydrogen, hydroxy or C₁₋₄-alkoxy, or a pharmacologically acceptable salt thereof. The invention also relates to a pharmaceutical composition comprising a compound of formula (I).

WO 02/45712 A1

NOVEL METHOD AND USE

Field of the Invention

The present invention relates to the use of selected compounds to antagonize or
5 inhibit GLP-1 activity in a mammal patient in need thereof, as well as to a pharmaceutical
composition comprising such antagonist(s).

Background of the Invention

Glucagon-like peptide 1(7-36)amide (GLP-1) is an intestinal hormone and
10 neurotransmitter that is involved in the control of metabolism and food intake. A major
function of the hormone appears to be the regulation of the amount of insulin released in
response to a meal, GLP-1 increasing the insulin secretion. It has therefore been proposed
that a molecule capable of augmenting the action of GLP-1, i.e. a GLP-1 agonist, should
be useful as an antidiabetic agent to lower elevated blood glucose levels in a mammal
15 serum.

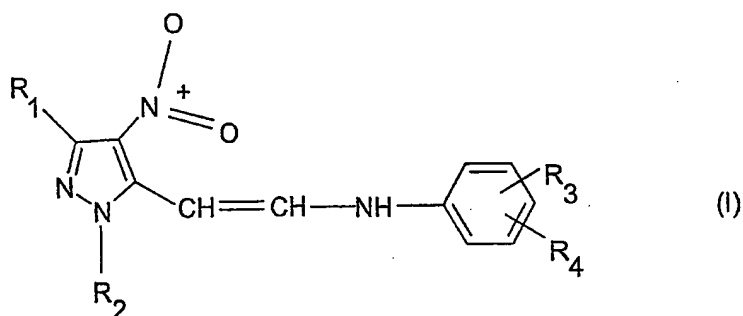
Conversely, a GLP-1 antagonist could be used to elevate the blood glucose level
in a subject afflicted with too low a blood glucose level. An exemplary such condition is
postprandial reactive hypoglycemia, such as in partially gastrectomised subjects (Toft-
Nielsen M. et al., Diabetologia 41(10):1180-6, 1998). Other disorders where a GLP-1
20 antagonist is believed to be useful include anorexia (Jensen P.B. et al., J. Clin. Invest.
102(2):503-10, 1998), and reduced intestinal motility and constipation (Tolessa T. et al.,
Digestive diseases and Sciences 43(10):2284-99, 1998). It has also been suggested that a
GLP-1 antagonist could be used to reduce symptoms in Alzheimer's disease, GLP-1
mediating the inhibition of beta-amyloid induced neural activation (Oka J.I. et al., SO
25 Neuroreport 10(8):1643-6, 1999).

Summary of the Invention

According to the present invention, a limited class of chemical compounds has
been found which are excellent antagonists of GLP-1 and therefore would be useful for
30 the treatment of diseases or disorders where inhibition of GLP-1 action would be
indicated.

Therefore, in one aspect thereof, the present invention provides a method of antagonizing (e.g., inhibiting) GLP-1 activity in a mammalian patient, comprising administering to said patient an effective amount of a compound of the general formula (I):

5



wherein:

R_1 and R_2 independently of each other are C_{1-4} alkyl,

R_3 is halogen, hydroxy, C_{1-4} -alkoxy or trifluoromethoxy, and

10 R_4 is hydrogen, hydroxy or C_{1-4} -alkoxy,

or a pharmacologically acceptable salt thereof.

In another aspect, the present invention provides a compound of formula (I) above for use as a pharmaceutical.

In still another aspect, the present invention provides a pharmaceutical
15 composition comprising a compound of formula (I) above and optionally a pharmaceutically acceptable carrier.

Yet another aspect of the present invention provides the use of a compound of formula (I) above for the preparation of a medicament for antagonizing GLP-1 activity in a mammalian patient.

20 This invention also features a method of treating a disorder where inhibition of GLP-1 activity is indicated. The method includes administering to a mammal subject in need thereof an effective amount of a compound of formula (I) above.

Further, this invention features a method of treating a disorder where inhibition of GLP-1 activity is indicated. The method includes administering to a mammal subject in

need thereof a pharmaceutical composition, wherein the pharmaceutical composition includes an effective amount of a compound of formula (I) above and a pharmaceutically acceptable carrier.

Also within the scope of this invention is a method for the manufacture of a medicament for antagonizing GLP-1 activity in a mammalian patient, characterized in that a compound of formula (I) above is used as the pharmaceutically active substance.

Brief Description of the Drawings

Fig. 1 is a diagram showing binding (cpm) of radiolabeled GLP-1 to a preparation of GLP-1 receptors in the presence of different concentrations (M) of the antagonist compound A.

Fig. 2 is a diagram showing cAMP production (pmol/dish) vs. antagonist concentration (microM) during stimulation of RINm5F cells with 3 nM GLP-1.

Fig. 3 is a diagram showing insulin release (ng/ml) vs. antagonist concentration (microM) during stimulation of RIN-m5F cells with 3 nM GLP-1 in the presence of four different antagonists.

Detailed Description of the Invention

As mentioned above, the invention resides in the finding of a limited class of compounds, i.e. compounds of formula (I) above, that are GLP-1 antagonists and which could therefore be used as GLP-1 antagonists for the treatment of a mammal subject, especially a human being (but also an animal, e.g. a pet), in need of such treatment. Disorders where administration of a GLP-1 antagonist would be indicated include, for example, postprandial reactive hypoglycemia, anorexia, reduced intestinal motility and constipation, and Alzheimer's disease.

In the compounds of formula (I), R₁ and R₂ are preferably methyl. R₃ is preferably halogen, hydroxy, methoxy or trifluoromethoxy. R₄ is preferably hydrogen, hydroxy or methoxy. Halogen is especially fluoro or chloro.

Specific compounds of the invention are:

4-chloro-2-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}phenol;

4-fluoro-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}benzene;

4-trifluoromethoxy-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}benzene; and

5 2,4-dimethoxy-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}benzene.

The compounds of formula (I) may be used as the compounds as such or, where appropriate, as the pharmacologically acceptable salts (acid or base addition salts) thereof. The compounds covered by formula (I) are also meant to include
10 stereochemically isomeric forms thereof, including optical isomers, such as enantiomers and racemates. Such compounds can also occur as cis- or trans-, *E*- or *Z*- double bond isomeric forms. All of the just-described isomeric forms are contemplated.

The pharmacologically acceptable addition salts as mentioned above are meant to comprise the therapeutically active non-toxic acid and base addition salt forms that the
15 compounds are able to form. Compounds that have basic properties can be converted to their pharmaceutically acceptable acid addition salts by treating the base form with an appropriate acid. Exemplary acids include inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulphuric acid, phosphoric acid; and organic acids such as acetic acid, propanoic acid, hydroxyacetic acid, lactic acid, pyruvic acid, glycolic
20 acid, maleic acid, malonic acid, oxalic acid, benzenesulphonic acid, toluenesulphonic acid, methanesulphonic acid, trifluoroacetic acid, fumaric acid, succinic acid, malic acid, tartaric acid, citric acid, salicylic acid, p-aminosalicylic acid, pamoic acid, benzoic acid, ascorbic acid and the like. Exemplary base addition salt forms are the sodium, potassium, calcium salts, and salts with pharmaceutically acceptable amines such as, for example,
25 ammonia, alkylamines, benzathine, and amino acids, such as, e.g. arginine and lysine. The term addition salt as used herein also comprises solvates which the compounds and salts thereof are able to form, such as, for example, hydrates, alcoholates and the like.

The compounds of formula (I) can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in
30 accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of one, or optionally more,

compound(s) of formula (I) in association with compatible pharmaceutically acceptable carrier materials, or diluents, as are well known in the art. The carriers may be any inert material, organic or inorganic, suitable for oral, enteral, rectal, percutaneous, subcutaneous or parenteral administration, such as: water, gelatin, gum arabicum, lactose, microcrystalline cellulose, starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmacologically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The compositions according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, pills, capsules, powders, syrups, elixirs, dispersable granules, cachets, suppositories and the like, in the form of sterile solutions, suspensions or emulsions for parenteral administration, sprays, e.g. a nasal spray, transdermal preparations, e.g. patches, and the like.

This invention relates to a method of treating a disorder where inhibition of GLP-1 activity is indicated. The method includes administering to a mammal subject (e.g., human) in need thereof an effective amount of one or more compounds of formula (I) above. The disorder includes, but is not limited to, postprandial reactive hypoglycemia, anorexia, reduced intestinal motility and constipation, and Alzheimer's disease.

"An effective amount" refers to an amount of a compound that confers a therapeutic effect on the treated subject. The therapeutic effect may be objective (i.e., measurably by some test or marker) or subjective (i.e., subject gives an indication of or feels an effect). The dose level of the compounds of formula (I), and the frequency of dosage of the specific combination, will vary depending on a variety of factors including the potency of each specific compound employed, the metabolic stability and length of action of that compound, the patient's age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the condition to be treated, and the patient undergoing therapy. The daily dosage may, for example, range from about 0.001 mg to about 150 mg per kilo of body weight, preferably from about 0.01 mg to about 100 mg per kilo of body weight, especially from about 0.1 to about 50 mg per kilo of body weight the compound of formula (I), administered singly or multiply in doses, e.g. dosages of from about 0.01 mg to about 25 mg each. Usually,

such a combined dosage is given orally but e.g. parenteral or rectal administration may also be chosen. A currently preferred oral daily dosage for a human subject is from about 1 to about 80 mg, preferably from about 1 to about 50 mg per day.

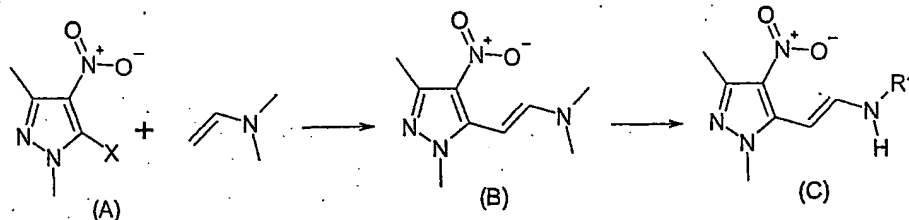
Several of the compounds of formula (I) above are commercially available.

- 5 Generally, compounds of formula (I) may be prepared by various routes as described in the following exemplary method schemes where "R1" denotes the terminal R₃/R₄-substituted phenyl group in the structural formula (I) above, and R₁ and R₂ in formula (I) both are methyl.

Method 1

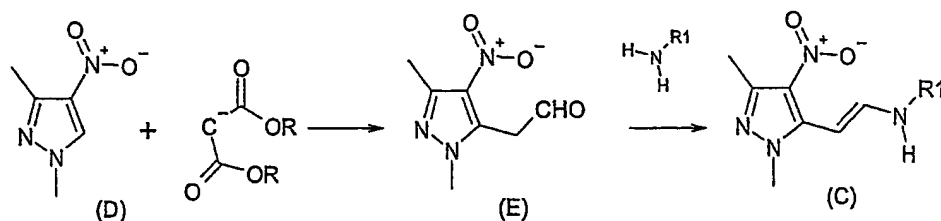
- 10 Displacement of X (X = e.g. Cl) in starting compound (A) in the reaction scheme below with an enamine gives compound (B) (similar to the displacement with cyanide described in Tet. (1979) 35; 1331). Treatment of (B) with an excess of a variety of enamines leads to analogues (C).

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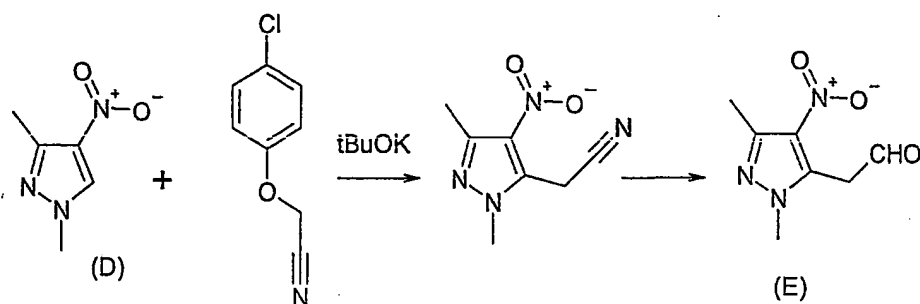
Method 2

- 20 Starting compound (D) in the reaction scheme below is subjected to a Michael type addition with the mono-anion of malonic diesters (JCS Perkin I, (1991) 5; 1077). Subsequent decarboxylation to give the corresponding acetic acid derivative and conversion thereof using standard methods gives the aldehyde (E), which by reaction with a suitable amine gives the desired analogue (C).



Method 3

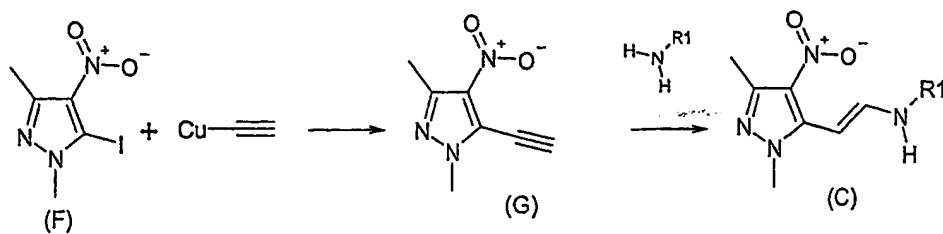
Starting compound (D) is reacted as shown in reaction scheme below to give the acetonitrile intermediate (Pol. J. Chem. (1977) 71, 10; 1413), which is converted to the corresponding aldehyde (E). The latter is then treated in same way as in Method 2 above to give the desired analogue (C).



10

Method 4

Starting compound (F) is subjected to a Michael type addition as shown in the reaction scheme below (Izv. Akad. Nauk SSSR, Ser. Khim. 1990 (9), 2089-2093) to give the intermediate (G) which is then reacted with a suitable amine to give the desired analogue (C).



The specific examples below are to be construed as merely illustrative, and not
limitative of the remainder of the disclosure in any way whatsoever. Without further
elaboration, it is believed that one skilled in the art can, based on the description herein,
5 utilize the present invention to its fullest extent. All publications cited herein are hereby
incorporated by reference in their entirety.

EXPERIMENTAL

The following compounds were used in the Examples below:

10 Compound A: 4-chloro-2-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-
yl)ethenyl]amino}phenol (formula (I) wherein R₁ and R₂ are each CH₃, R₃ is 5-Cl and
R₄ is 2-OH).

Compound B: 4-fluoro-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-
yl)ethenyl]amino}benzene (formula (I) wherein R₁ and R₂ are each CH₃, R₃ is 4-F and
15 R₄ is H).

Compound C: 4-trifluoromethoxy-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-
yl)ethenyl]amino}benzene (formula (I) wherein R₁ and R₂ are each CH₃, R₃ is 4-OCF₃
and R₄ is H)

Compound D: 2,4-dimethoxy-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-
20 yl)ethenyl]amino}benzene (formula (I) wherein R₁ and R₂ are each CH₃, R₃ is 4-
methoxy and R₄ is 2-methoxy).

These compounds are commercially available and were obtained from the French
firm Ambinter, 46 quai Louis Bleriot, F-75016, Paris.

25

EXAMPLE 1

Inhibition of ¹²⁵I-GLP-1 binding to human recombinant GLP-1 receptors

Wheatgerm agglutinin scintillation proximity assay (SPA) beads (500 mg) from
Amersham (RPNQ 0001) were diluted into 50 ml of assay buffer (Assay buffer consisted
of 150 mM NaCl, 10 mM MgCl₂, 1 mM EDTA, and 20 mM HEPES, pH 7.4). The SPA

beads were combined (1:1 v/v) with a crude membrane preparation from COS7 cells transfected with the human GLP-1 receptor at a concentration of 30 µg/ml/well. These cells (COSHGLPr, clone #16) were grown in Dulbecco's Modified Eagle Medium with high glucose (DMEM Gibco, #11965-092) supplemented with 10% heat-inactivated fetal bovine serum (Gibco, #1600-044), 2mM L-Glutamine (Gibco #25030-081), and 10 µg/ml Gentamicin (Gibco #15710-064) with 705 µg/ml Geneticin (G418 sulfate, Gibco) (DMEM complete). The mixture was incubated for two hours at room temperature with constant rotation. The free membranes were washed away by centrifuging the mixture for 5 minutes at 800 rpm in a table-top GLC1 (Sorvall) centrifuge. The supernatant was discarded and the pellet was resuspended in 50 ml assay buffer + 0.1% bovine serum albumin. Aliquots of 100 µl of the membranes containing 1 mg SPA beads were placed into a well of a 96-well microtiter plate (WALLAC 1450-501). Compound A was dissolved in DMSO to give a 5 mM solution that was further diluted in assay buffer. Aliquots of 50 µl from each dilution were added to wells containing SPA beads. GLP-1 (7-36) amide (Sigma) was added to the wells at 10 µM final concentration for wells to measure non-specific binding. Finally, 50 µl of ¹²⁵I-GLP-1 (Amersham IMQ0284; 1600-2000 Ci/mmol; 46000 to 50000 cpm/well). The plate was sealed and incubated in a shaker for 1 h at room temperature. The plates were counted approximately 10 h later in a Microbeta Trilux liquid scintillation counter (WALLAC). The concentrations causing 50% inhibition of binding were estimated by non-linear regression to a one-site binding model. Binding constants (K_i) were calculated with the Cheng-Prushoff equation (Cheng YC and Prushoff WH, Biochem Pharmacol 22:3099, 1973). The results are shown in Fig. 1. As appears therefrom, increasing concentrations of compound A inhibited the binding of GLP-1 to its receptor with a K_i value of approximately 1 µM.

25

EXAMPLE 2

Inhibition of GLP-1 induced cAMP signaling

GLP-1 signaling was measured in RIN-m5F insulinoma cells, which possess endogenous GLP-1 receptor coupled to adenylate cyclase (Göke R. *et al.*, Mol Cell Endocrinol 85:C39-C44). The cells were obtained from the American Type Culture

30

Collection (ATCC, #203641 F13132) and grown in RPMI 1640 (GIBCO, #21870-076) supplemented with 2 mM L-glutamine, 10% heat inactivated fetal bovine serum, and 10 μ g/ml Gentamicin.

RIN-m5F cells were plated in 12 well plates at a density of 2.0×10^5 cells per ml and grown for 4 days in complete RPMI 1640 with 10% fetal bovine serum; the medium was changed the day before experiment. The cells were from 70-90% confluent at the time of the experiment. On the day of the experiment, the incubation medium was removed and the cells were washed with fresh serum-free RPMI 1640 containing 0.1% bovine serum albumin (serum-free medium). One ml DMEM complete with 1 mM 3-isobutyl-1-methylxanthine (Sigma) was added and the plates were placed at 37°C and 5.0% CO₂ for 15 minutes before initiation of the experiment. Fresh compounds were acquired and dissolved as 10 mM solutions in DMSO. A further 1:10 dilution was prepared in DMEM and after the incubation period, the compounds were added to the wells at 30 μ M final concentration. The final concentration of DMSO was always 0.3%. The wells were treated with or without GLP-1 (3 nM). The plates were then incubated at 37°C and 5.0% CO₂ for 15 minutes. The medium was removed and cells were washed twice with 1 ml "cold DMEM no serum". For lysis of the cells, 0.5 ml of the 50 mM HCl solution was added to each well and let stand on ice for 1 hour. The solution was mixed well and quantitatively transferred to microcentrifuge tubes with 1 wash of 0.5 ml of the 50 mM NaOH solution. The neutralized cell extracts were centrifuged for 15 min at 15,000 rpm at 4°C (Tomy centrifuge). The supernatants were transferred to microcentrifuge tubes and the cellular debris was discarded. An aliquot was diluted with cAMP assay buffer and 100 μ l was assayed in duplicate in cAMP SPA system (dual range) from Amersham (RPA 538) using the protocol for cAMP concentrations between 0.2 and 12.8 pmol/well as outlined by the manufacturer. The results are shown in Fig. 2. As appears therefrom, compound A concentration dependently decreased GLP-1 stimulated cAMP production to a level close to that obtained in the absence of GLP-1.

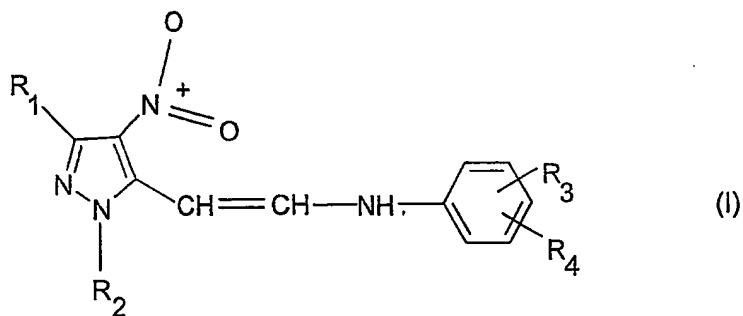
EXAMPLE 3

Inhibition of GLP-1 stimulated insulin release

The RIN-m5F cells were grown as in Example 2. The cells were plated in 96-well plates (10,000 per well) at a density of 2×10^5 cells per ml and grown for 3 days. The culture medium was changed the day before the experiment. On the day of the experiment, the medium was removed and replaced with serum-free RPMI 1640 containing 0.1% bovine serum albumin (serum-free medium). Dilutions of compounds prepared in serum-free medium from 10 mM DMSO stock solutions to give final concentrations from 0.1 μ M to 30 μ M were added. The cells were stimulated with 3 nM GLP-1 in a total volume of 200 μ l for 1 h and the concentration of insulin in the medium was measured in an ELISA (Mercodia AB). The insulin release in the presence of medium was 6.3 ± 1.4 ng/ml and 10.5 ± 1.4 ng/ml in the presence of 3 nM GLP-1. The results (mean of triplicate cultures in one experiment) are shown in Fig. 3. As appears therefrom, increasing concentrations of compound A, B, C, or D each causes a substantial reduction of the GLP-1 induced insulin release, i.e. that the compounds effectively antagonize the activity of GLP-1.

CLAIMS

1. A method of antagonizing GLP-1 activity in a mammalian subject, comprising administering to said subject an effective amount of a compound of the general formula (I):



wherein

R_1 and R_2 independently of each other are C_{1-4} alkyl,

R_3 is halogen, hydroxy, C_{1-4} -alkoxy or trifluoromethoxy,

R_4 is hydrogen, hydroxy or C_{1-4} -alkoxy,

or a pharmacologically acceptable salt thereof.

2. The method according to claim 1, wherein R_1 and R_2 are methyl.

3. The method according to claim 1 or 2, wherein R_3 is halogen, hydroxy, methoxy or trifluoromethoxy.

4. The method according to any one of claims 1-3, wherein R_4 is hydrogen, hydroxy or methoxy.

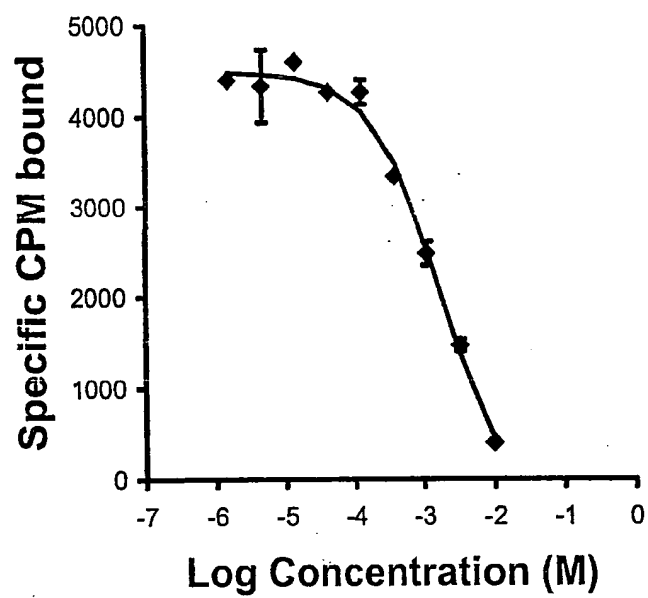
5. The method according to any one of claims 1-4, wherein R_4 is hydroxy or C_{1-4} -alkoxy.

6. The method according to claim 1 or 3, wherein halogen is fluoro or chloro.
7. The method according to any one of claims 1-5, wherein the compound is:
- 5 4-chloro-2-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}phenol;
4-fluoro-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}benzene;
4-trifluoromethoxy-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}benzene; or
10 2,4-dimethoxy-1-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}benzene.
8. The method according to any one of claims 1-6, wherein the compound is:
4-chloro-2-{[(E)-2-(1,3-dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]amino}phenol.
- 15 9. The method according to any of the preceding claims, wherein GLP-1 is antagonized to treat a disease selected from postprandial reactive hypoglycemia, anorexia, reduced intestinal motility and constipation, and Alzheimer's disease.
- 20 10. A pharmaceutical composition comprising a compound of formula (I) in claim 1 and optionally a pharmaceutically acceptable carrier.
11. Use of a compound of formula (I) in claim 1 in the manufacture of a pharmaceutical preparation for the treatment of a disorder where inhibition of
25 GLP-1 is indicated.
12. Use of a compound according to claim 11, wherein the disorder is postprandial reactive hypoglycemia.
- 30 13. Use of a compound according to claim 11, wherein the disorder is anorexia.

14. Use of a compound according to claim 11, wherein the disorder is reduced intestinal motility and constipation.
15. Use of a compound according to claim 11, wherein the disorder is Alzheimer's disease.
16. Use of a compound according to claim 11, wherein the mammal subject is a human.
17. A pharmaceutical composition used in the treatment of a disorder where inhibition of GLP-1 activity is indicated, wherein the pharmaceutical composition includes an effective amount of the compound of formula (I) in claim 1 and a pharmaceutically acceptable carrier.

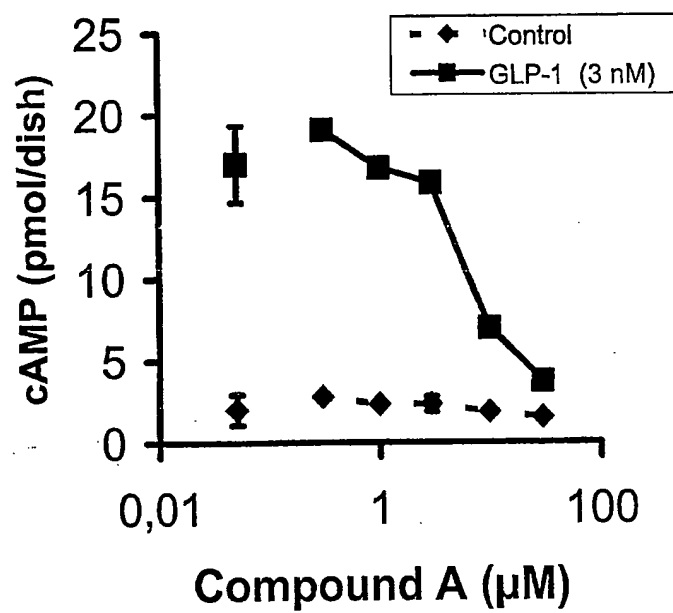
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Fig. 1



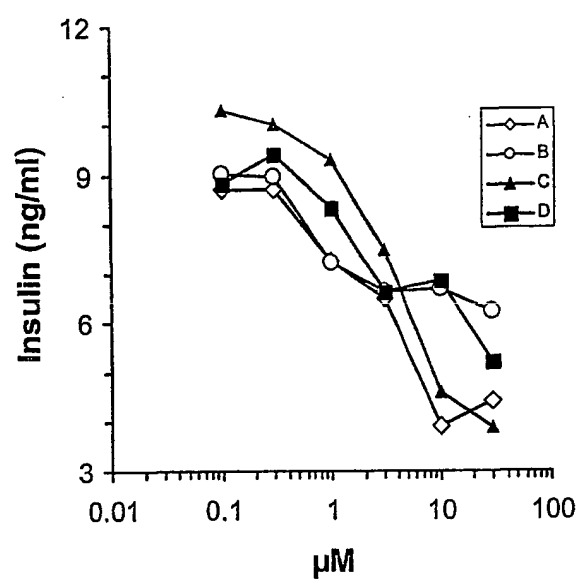
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Fig. 2



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Fig. 3



INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02680

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61K 31/415, A61P 3/10, A61P 3/04, A61P 1/10, A61P 25/28, A61P 5/48
 // C07D 231/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS.DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	STN International, file CHEMCATS, accession no. 2001:212848, Ambinter: Screening Collection" 20010531, "Benzenamine, N-[2-(1,3- dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]-4- (trifluoromethoxy)-", RN 321553-17-7 --	1-17
P,A	STN International, file CHEMCATS, accession no. 2001:212307, Ambinter: Screening Collection, 20010531, "Phenol, 4-chloro-2-[[2- (1,3-dimethyl-4-nitro-1H-pyrazol-5-yl) ethenyl]amino]-", RN 320424-79-1 --	1-17

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
 "E" earlier application or patent but published on or after the international filing date
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 "O" document referring to an oral disclosure, use, exhibition or other means
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

1 March 2002

Date of mailing of the international search report

11 -03- 2002

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/02680

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	STN International, file CHEMCATS, accession no. 2001:212302, Ambinter: Screening Collection, 20010531, "Benzenamine, N-[2-(1,3- dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]-2,4- dimethoxy-", RN 320424-74-6 --	1-17
P,A	STN International, file CHEMCATS, accession no. 2001:212296, Ambinter: Screening Collection, 20010531, "Benzenamine, N-[2-(1,3- dimethyl-4-nitro-1H-pyrazol-5-yl)ethenyl]-4- fluoro-", RN 320424-68-8 --	1-17
A	STN International, File CAPLUS, CAPLUS accession no. 1999:382989, Document no. 131:165408, Meurer, Janet A. et al: "Properties of native and in vitro glycosylated forms of the glucagon-like peptide-1 receptor antagonist exendin(9-39)"; Metab., Clin. Exp. (1999), 48(6), 716-724 --	1-17
A	WO 0033839 A1 (AGOURON PHARMACEUTICALS, INC), 15 June 2000 (15.06.00) --	1-17
A	WO 0069849 A1 (ORTHO-MCNEIL PHARMACEUTICAL, INC.), 23 November 2000 (23.11.00), the claims --	1-17
A	WO 9303714 A2 (THE UPJOHN COMPANY), 4 March 1993 (04.03.93), the claims; page 4, line 34 - page 19, line 5 --	1-17
A	EP 0142190 A2 (JANSSEN PHARMACEUTICAL. N.V.), 22 May 1985 (22.05.85), the claims -- -----	1-17

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/02680

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-9
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/02680

Claims 1-9 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

28/01/02

International application No.
PCT/SE 01/02680

Patent document cited in search report				Publication date		Patent family member(s)	Publication date
WO	0033839	A1	15/06/00	AU	1751800	A	26/06/00
				BR	9916965	A	06/11/01
				EP	1137413	A	04/10/01
WO	0069849	A1	23/11/00	AU	4690600	A	05/12/00
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				DK	162984	B,C	06/01/92
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				FI	85854	B,C	28/02/92
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